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**FOR: JONATHAN WOODSON, M.D., ASSISTANT SECRETARY OF DEFENSE
(HEALTH AFFAIRS)**

**SUBJECT: Recommendations Regarding the Addition of Tranexamic Acid to the Tactical
Combat Casualty Care Guidelines 2011-06**

EXECUTIVE SUMMARY

Traumatic hemorrhage is the leading cause of preventable death on the battlefield. A comprehensive review of the literature (as provided in this report) found that the antifibrinolytic tranexamic acid (TXA) has proven to decrease all cause mortality following major trauma. In trauma patients experiencing severe hemorrhage on the battlefield, tranexamic acid has the potential to reduce both mortality and morbidity. In light of these findings, the Defense Health Board recently approved a recommendation for the addition of tranexamic acid to the Tactical Combat Casualty Care (TCCC) guidelines.

INTRODUCTION

TCCC is a set of trauma care guidelines customized for use in the pre-hospital combat setting. The guidelines identify three stages of care: (1) care under fire; (2) tactical field care; and (3) tactical evacuation care. TCCC is currently used in training for medics by all Services in the Department of Defense (DoD) and by many U.S. coalition partners.^{1,2} The Committee on Tactical Combat Casualty Care (CoTCCC), a work group of the Defense Health Board (DHB) Trauma and Injury Subcommittee, performs a quarterly review of current evidence demonstrating the successes and shortcomings of the TCCC Guidelines, and considers proposed updates and revisions.^{1,2}

The CoTCCC began reviewing the data supporting the use of TXA for trauma patients in 2010. However, it was not until April 5, 2011, when the subcommittee was provided pre-publication data from the Military Application of Tranexamic Acid in Traumatic Emergency and Resuscitative Surgery (MATTERS) study, that the subcommittee felt the evidence warranted a change in the TCCC guidelines. The CoTCCC submitted the recommendation that TXA use be expanded to the prehospital setting as part of the TCCC guidelines on August 2, 2011. Subsequently, the Trauma and Injury Subcommittee gave approval of the recommendation on August 3, 2011. On August 8, 2011, the DHB approved the recommendation by unanimous vote.

BACKGROUND

This recommendation utilizes the American College of Cardiology/American Heart Association grading schema for level of evidence and class of recommendation to support the guideline revision recommendation for TXA administration in Tactical Field Care and Tactical Evacuation Care incorporating recent literature and expert opinion.³

In addition to previous Level B and C data supporting TXA use which was derived from Phase I and Phase II clinical trials, there is now Level A evidence supporting the addition of TXA to the guidelines for the treatment of trauma-induced hemorrhage. The CRASH-2⁴ study is a large prospective randomized controlled clinical trial involving civilian trauma patients. The MATTERS⁵ study is a retrospective case control study involving well-matched combat casualties who received care at the busiest medical treatment facility in United States Central Command (CENTCOM) that employed standardized advanced treatment and resuscitation protocols that reflected the current standard of care. Although the MATTERS study is not a randomized controlled trial, it addresses the shortcomings of the CRASH-2 study and is directly applicable to combat-related trauma.

Classes of Recommendation and Level of Evidence

I. Early administration of 1 gram of TXA to casualties who are anticipated to receive blood transfusions

a. Recommendation: **Class I**

b. Specified/Implied Actions:

- Hemorrhage is a common contributor to death in combat casualties (**Level B**)
- Hemostatic resuscitation improves survival (**Level B**)
- Antifibrinolytics (specifically TXA) have been shown to decrease bleeding in hemophilia and menorrhagia (**Level B**)
- Tranexamic acid has FDA approval to decrease bleeding in hemophilia and menorrhagia (**Level B**)
- Tranexamic acid has been shown to benefit civilian trauma patients (**Level B**)
- Tranexamic acid has been shown to benefit combat casualties when a rigorous hemostatic resuscitation is followed (**Level B**)
- Early administration (<3 hours) of TXA after injury appears to improve survival (**Level B**)
- Arrival to Level II and III care facilities in a combat setting within three hours of injury are not guaranteed (**Level C**)
- Storage of TXA in field conditions will be problematic with its temperature limitations (**Level C**)
- Identification of who needs TXA, administration of TXA and monitoring for complications requires skills of an advanced practice medic (**Level C**)

Overall Level of Evidence: B

DISCUSSION

Hemorrhage is the leading cause of preventable death among combat casualties. Patients who require a massive blood transfusion (greater than 10 PRBCs within 24 hours) have an improved survival when an early aggressive hemostatic resuscitation is followed. Patients at the greatest

risk of exsanguination often present with clinically significant coagulopathy that has recently been linked to systemic anticoagulation through a Protein C-dependent pathway, and activation of fibrinolysis.⁶ The activation of fibrinolysis accompanying the massive generation of thrombin in the period immediately following trauma has been well described and is readily observed by the elevated levels of D-dimers, fibrin split products (FSP) and plasmin-antiplasmin complexes found in blood samples drawn from trauma patients on presentation.⁷ Fibrinolysis can occasionally overwhelm clot formation following trauma, a phenomenon that can be directly observed in real time by thromboelastography or rotational thromboelastometry. Such hyperfibrinolysis occurs only in the most severely injured patients (approximately 4 percent of trauma patients in major civilian US trauma centers) and portends extremely poor outcomes.^{8,9}

Coagulation system responses to trauma and surgery are broadly similar and activation of fibrinolysis has been observed in surgical patients. The safety and efficacy of TXA to treat trauma patients was recently evaluated in a large randomized, placebo-controlled clinical trial, "Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage" (CRASH-2)³. In this trial, 20,211 adult trauma patients in 274 hospitals in 40 countries with, or at risk of, significant bleeding (HR>110, SBP<90, clinical judgment) were randomized to either TXA or placebo administered as a loading dose of 1 gram over 10 minutes followed by an infusion of 1 gram over 8 hours. The primary outcome was death in hospital within 4 weeks of injury. Secondary outcomes included vascular occlusive events, transfusions, and surgical interventions. Patients were randomized and treated within 8 hours of injury. Further, patients were excluded from randomization only if the treating physician considered the patient to have either a clear indication for use of TXA or a clear contraindication. This randomization scheme reflects application of the uncertainty principle, or clinical equipoise in decision-making. Only 14 patients out of 20,225 screened were excluded from randomization, because they died before they could be randomized.¹⁰ The treatment and placebo groups were well-balanced across a wide range of prognostic variables. The overall mortality rate in the cohort studied was 15.3 percent, of whom 35.3 percent died on the day of randomization. A total of 1063 died due to hemorrhage; 59.9 percent of these died on the day of randomization. A subgroup at particularly high risk of death included those patients presenting with a SBP<75 (3,161 of 20,125; 15.7 percent). Overall, this study included a large and very diverse trauma population, with most patients facing a relatively low mortality risk. Nevertheless, over 3,000 patients in the study would likely have been candidates for treatment under a damage control resuscitation (and possibly massive transfusion) procedure. The authors reported that TXA use resulted in a statistically significant reduction in the relative risk of all-cause mortality of 9 percent (14.5 percent vs. 16.0 percent, RR 0.91, CI 0.85-0.97; p = 0.0035). This 1.5 percent absolute risk reduction means that one would have to treat 67 trauma patients with TXA to prevent one from dying of any cause (number needed to treat = 1/absolute risk reduction). Note that this NNT reflects the underlying mortality risk in the CRASH-2 study (15 percent). The authors also reported a reduction in relative risk of death due to bleeding of 15 percent (4.9 percent vs. 5.7 percent, RR 0.85, CI 0.76-0.96; p = 0.0077). Similarly, the authors reported a relative risk reduction in death due to bleeding on the day of randomization of 20 percent (2.8 percent vs. 3.5 percent, RR 0.80, CI 0.68-0.93; p = 0.0036). It was in this group of most severely injured patients that use of TXA was associated with the greatest reduction in risk of death. Further subgroup analysis suggested that the benefit of TXA was greater in patients treated within 3

hours of injury compared to those treated later and in patients with a presenting systolic blood pressure of ≤ 75 mmHg compared to those with normal systolic blood pressures. There was no difference in rate of vascular occlusive events between the two arms of the study (1.7 percent for TXA vs. 2.0 percent for placebo, $p = 0.084$). No unexpected adverse events were reported. There were no differences in need for transfusion or surgery between the two arms (blood product transfused in 50.4 percent of patients for TXA vs. 51.3 percent for placebo, $p = 0.21$; any surgery in 47.9 percent of patients for TXA and 48.0 percent for placebo, $p = 0.79$). A recent post-hoc analysis of the CRASH-2 data suggests that the greatest benefit of TXA administration is likely to occur when patients receive the medication soon after injury. In this analysis, TXA given between 1 and 3 hours post-trauma reduced the risk of death due to bleeding by 21 percent (147/3037 [4.8 percent] vs. 184/2996 [6.1 percent], RR 0.79, CI 0.64-0.97; $p=0.03$). Treatment given after 3 hours seemed to increase the risk of death due to bleeding (144/3272 [4.4 percent] vs. 103/3362 [3.1 percent], RR 1.44, CI 1.12-1.84; $p=0.004$).¹¹

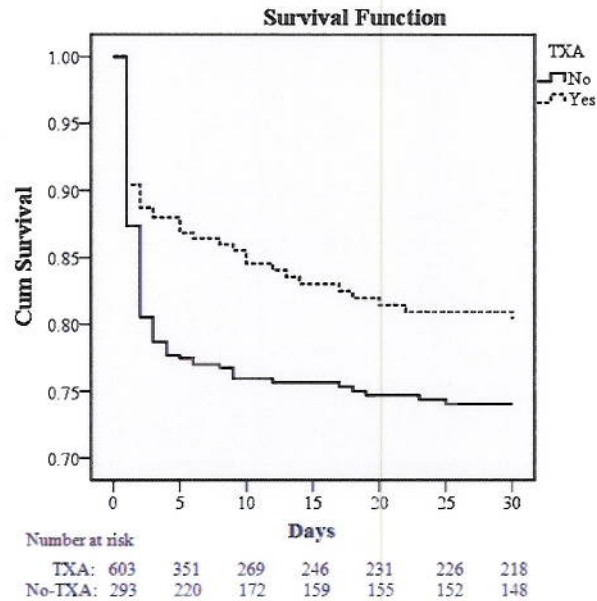
Of note, the Cochrane Collaboration conducted a review of antifibrinolytic drugs for acute traumatic injury, concluding that, based on the results of the CRASH-2 study, TXA reduces all-cause mortality in bleeding trauma patients with no apparent increase in the risk of vascular occlusive events. The review additionally notes that the quality of the evidence supporting the use of TXA for trauma is high (RR .90, CI 0.85-0.97).¹²

TXA Experience in Combat-Related Hemorrhage

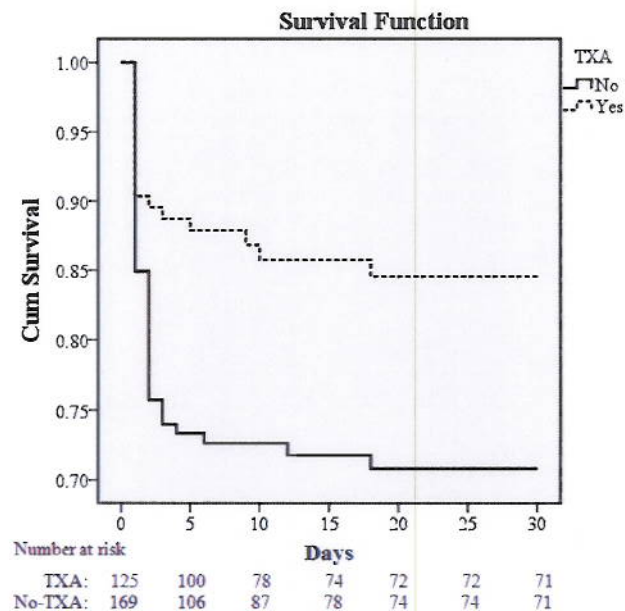
A recent registry-based study of combat injured troops receiving blood in Afghanistan (January 2009 - December 2010) at the Bastion Role 3 facility has demonstrated findings supportive of TXA use in this population. In a review of 896 combat casualties treated at Bastion over this time frame, 32.7 percent ($N=293$) received TXA (mean \pm SD dose: 2.3 ± 1.3 g) while 67.2 percent ($N=603$) did not receive TXA. In the overall cohort, the TXA group was more severely injured (ISS: 25.2 ± 16.6 vs. 22.5 ± 18.5 ; $p < 0.001$), required more blood (11.8 ± 12.1 vs. 9.8 ± 13.1 pRBC units; $p < 0.001$), and had a lower Glasgow Coma Score (GCS) (7.3 ± 5.5 vs. 10.5 ± 5.5 ; $p < 0.001$) and initial systolic blood pressure (112 ± 29.1 vs. 122.5 ± 30.3 mmHg), but also had a lower unadjusted mortality than the no-TXA group (17.4 percent vs. 23.9 percent; $p=0.028$). In the massive transfusion cohort ($N=321$; 24 hour transfusion: 21.9 ± 14.7 pRBC; 19.1 ± 13.3 FFP and 3.5 ± 3.2 apheresis platelet units), mortality was also lower in the TXA (mean \pm SD dose: 2.4 ± 1.4 g) compared to the no-TXA group (14.4 percent vs. 28.1 percent; $p=0.004$). In a multivariate regression model, TXA use in the massive transfusion cohort was independently associated with survival (odds ratio: 7.28; 95 percent confidence interval: 3.02-17.32. For all patients requiring at least one unit of blood after combat injury, patients receiving TXA had higher rates of DVT (2.4 percent vs. 0.2 percent, $p = 0.001$) and PE (2.7 percent vs. 0.3 percent, $p = 0.001$), but were also more likely to have injury patterns associated with higher risk of thromboembolic events; including higher mean ISS (25 vs 23, $p < 0.001$), more severe extremity injuries (extremity AIS ≥ 3 66.6 percent in TXA group, 47.3 percent non-TXA, $p < 0.001$), and more commonly GCS ≤ 8 (63.3 percent vs. 35.6 percent, $p < 0.001$). These survival benefit findings associated with TXA use support the hypothesis that the use of this adjunct, in conjunction with component-based resuscitation

SUBJECT: Addition of Tranexamic Acid to the Tactical Combat Casualty Care Guidelines
2011-06

following combat injury, is associated with improved survival. This association is most prominent in those requiring massive transfusion.⁴



Kaplan-Meier survival curve of the overall cohort, patients receiving TXA or no-TXA, $p = 0.006$ (Wilcoxon Statistic)⁵



Kaplan-Meier survival curve of the massive transfusion group receiving TXA^{MT} or no-TXA^{MT}, $p = 0.004$ (Wilcoxon Statistic)⁵

TXA Mechanism

TXA is an anti-fibrinolytic that inhibits both plasminogen activation and plasmin activity, thus preventing clot break-down rather than promoting new clot formation. TXA (trans-4-(aminomethyl) cyclohexanecarboxylic acid) is a small molecule (MW 157.2) inhibitor of plasminogen activation, and inhibitor of plasmin activity. It occupies the lysine-binding sites on plasminogen thus preventing its binding to lysine residues on fibrin. This reduces plasminogen activation to plasmin. Similarly, blockade of lysine-binding sites on circulating plasmin prevents binding to fibrin, and thus prevents clot break-down.

TXA is 10 times more potent *in vitro* than an older drug of the same class, aminocaproic acid. At therapeutically relevant concentrations, TXA does not affect platelet count or aggregation or coagulation parameters. It is excreted largely unchanged in urine and has a half-life of about 2 hours in circulation. Dosing should be adjusted for renal impairment, but no adjustment is needed for hepatic impairment. TXA (intravenous trade name: Cyklokapron) is supplied in ampoules of 1000 mg in 10 ml water for injection.

Food and Drug Administration Position

Intravenous administration of TXA (under the brand name Cyklokapron[®], Pfizer) was approved by the Food and Drug Administration (FDA) in 1986 for short-term use (2-8 days) for prevention or reduction of bleeding in patients with hemophilia undergoing dental procedures. The FDA approved use of the oral form of TXA (Lysteda[™], Ferring Pharmaceuticals) for menorrhagia (to control heavy menstrual cyclic bleeding) in 2009.

Although TXA is an FDA-approved drug and has undergone regulatory and clinical testing, the FDA-approved indication does not currently include stopping uncontrolled hemorrhage in severe trauma patients. The antifibrinolytic effect of tranexamic acid was first reported in 1966.¹³ TXA has been studied in many clinical settings, including hemophilia,¹⁴ intraoperative and postoperative bleeding,¹⁵ gastrointestinal hemorrhage,¹⁶ traumatic hyphema¹⁷ and hereditary angioedema.¹⁸

It has been studied in randomized trials to control bleeding during surgery, and most recently in trauma as discussed above. It is widely used in non-trauma surgeries and has been used on a limited basis by at least one major U.S. civilian trauma center (Massachusetts General Hospital).¹⁹ It has been given at the discretion of individual providers, based on their assessment of the clinical condition of the patient.

Potential Adverse Events with TXA

Adverse events associated with TXA use have been reported. These include acute gastrointestinal disturbances (nausea, vomiting and diarrhea, generally dose-related), visual disturbances (blurry vision and changes in color perception, especially with prolonged use), and occasional thromboembolic events (e.g., deep venous thrombosis, pulmonary embolism, generally observed in the setting of active intravascular clotting such as thrombotic DIC). Its use

is thus contraindicated in the settings of acquired defective color vision and active intravascular clotting. TXA should be used carefully in the setting of urinary tract bleeding as ureteral obstruction due to clotting has been reported. TXA should not be given with activated prothrombin complex concentrate or factor IX complex concentrates as this may increase the risk of thrombosis. Another adverse risk noted in a retrospective review in patients who had undergone pulmonary endarterectomy with hypothermia was an increase in seizure activity (when compared to aprotinin) in patients without structural brain lesions (7 versus 0, $p=0.02$)²⁰ The doses given were high dose (on the order of 3-6 times the dose used in the two trauma studies).

Considerations for Use

TXA has been studied in patients with subarachnoid hemorrhage (SAH). TXA was shown to reduce bleeding in SAH, but increase cerebral ischemia, possibly due to vasospasm or increased microvascular thrombosis. Since TXA use had no effect on mortality or quality of life in these studies, its use is not recommended in this population. At this time, there is no role for TXA or other antifibrinolytics in managing SAH. It should be noted that treatment with TXA in these studies was modeled on the prolonged (3-4 times per day for 2-8 days) dosing used in hemophilia. A dosing regimen shorter in duration might avoid this outcome, and remains a topic for further investigation.

It is worth noting, as discussed above, that the relative contraindication to using antifibrinolytics in SAH was known prior to the initiation of CRASH-2. Thus, it is possible that treating physicians tended to exclude patients with traumatic brain injury (TBI) from trial enrollment. Nevertheless, about 18 percent of patients had a GCS score of 3-8 (17.8 percent for TXA, 18.2 percent for placebo), probably indicating severe TBI, and 13.4 percent had GCS scores of 9-12 ($p>0.05$, NS, for both groups), indicating moderate TBI. Mild or no TBI (GCS 13-15) was present in 68.7 percent (TXA) and 68.3 percent (placebo). While GCS scores can be depressed for a variety of reasons such as global hypoperfusion, it would be reasonable to expect that a substantial fraction of trauma patients with depressed GCS had in fact sustained a TBI. The authors did report that death from head injury was the same in both groups (6.0 percent for TXA and 6.2 percent for placebo, RR 0.97, CI 0.87-1.08, $p=0.6$). They also reported that stroke rates (0.6 percent for TXA and 0.7 percent for placebo) and neurosurgery rates (10.3 percent for TXA and 10.5 percent for placebo) were similar between the groups. These data are reassuring; if a major safety concern were present for perhaps one third of the patients in the trial (those with depressed GCS among whom TBI patients are common) a negative effect on outcomes would be expected.

Critics of the CRASH-2 study have noted that it would have been helpful to know outcomes for patients' with TBI, since TXA has not proven to be beneficial in SAH. As a result, the CRASH-2 Intracranial Bleeding Study was a prospective randomized controlled trial nested within the CRASH-2 trial, conducted to quantify the effects of an early short course (1 g over 10 minutes, within 8 hours of injury) of TXA on intracranial hemorrhage in patients with TBI.²¹ This portion of the trial involved 270 patients who had a documented head injury (GCS ≤ 14 and an abnormal CT scan of the head) and were at risk of significant extracranial bleeding (133 patients

allocated to TXA and 137 allocated to placebo), and found new focal cerebral ischemic lesions occurred in 6 (5 percent) patients in the TXA group, compared to 12 (9 percent) in the placebo group (RR 0.51, CI 0.18-1.44). Mortality was higher in the placebo group (18 percent for placebo, 11 percent for TXA, RR 0.47, CI 0.21-1.04). In addition, mean total hemorrhage growth was higher in the placebo group. This trial shows that neither moderate benefits nor moderate harmful effects can be excluded, however, the analyses suggest that TXA might improve outcomes for patients with TBI and should be further evaluated in future research. The CRASH-3 trial will further examine the effectiveness of the early administration of a short course of TXA in patients with TBI.

Hextend[®] is commonly used as a resuscitation fluid in trauma patients. Several studies have demonstrated that this product may interfere with hemostasis through a number of mechanisms including fibrinolysis. Due to poorly defined potential interactions between Hextend[®] and TXA, which may blunt the antifibrinolytic activity of TXA, TXA should not be given through the same IV as Hextend[®], and Hextend[®] should not be used as a carrier fluid for this medication.

Use of TXA in conjunction with pro-coagulant drugs sometimes administered to trauma patients, such as recombinant factor VIIa (Novoseven) or activated prothrombin complex concentrate (APCC), could result in thrombotic complications. Of note, only 17 patients enrolled in the CRASH-2 trial received Novoseven (13 in the TXA group and 4 in the placebo group). It is also possible that a subgroup of patients not identified in the CRASH-2 trial, such as those with TBI, may be at particularly high risk of thrombotic or other complications if treated with TXA. It is very reassuring, however, that no increase in vascular occlusive events was observed in this study, despite the significantly increased baseline risk of such complications in this population. The rate of deep vein thrombosis reported is difficult to interpret due to the lack of a consistent screening procedure, and the variable clinical importance of this complication. However, the rates of myocardial infarction, stroke and pulmonary embolism may be more informative. These complications are relatively simple to diagnose, and are of clinical importance. None of these complications were more common in the treatment arm, while myocardial infarction was significantly less common in the TXA group ($p=0.035$). These data strongly argue against a safety problem with respect to vascular occlusive events.

Guidelines for Use

TXA (intravenous trade name: Cyklokapron) is supplied in ampoules of 1000 mg in 10 ml water for injection. The CRASH-2 guidelines for TXA administration included:

- a. Infuse 1 gram of TXA in 100 ml of 0.9 percent Normal Saline (NS) over 10 minutes intravenously (more rapid injection has been reported to cause hypotension). Hextend[®] should be avoided as a carrier fluid.
- b. Infuse a second 1-gram dose intravenously over 8 hours infused with 0.9 percent NS carrier.
- c. ***There are presently no data from randomized controlled trials to support administration of further doses to trauma patients. However, case control studies support the administration of up to three grams of TXA.***

SUBJECT: Addition of Tranexamic Acid to the Tactical Combat Casualty Care Guidelines
2011-06

In the MATTERS study, which more closely reflects the combat trauma population, administration guidelines included:

- a. Infuse 1 gram of TXA in 100 ml of 0.9 percent NS via intravenous push.
- b. Infuse 1 to 2 additional grams of TXA during the subsequent resuscitation.

TXA should be stored at room temperature (15-30 °Celsius / 59-86° Fahrenheit).

Guidelines for Administration in the Deployed Setting

The early use of TXA should be strongly considered for any patient requiring blood products in the treatment of combat-related hemorrhage and is most strongly advocated in patients judged likely to require massive transfusion (e.g., significant injury and 3 or 4 risk factors/indicators of massive transfusion).

Use of TXA within 3 hours of injury is associated with the greatest likelihood of clinical benefit. **The greatest benefit was seen when TXA was administered within 1 hour of wounding.** Due to this time constraint, the uncertainty of battlefield evacuation, and a good safety profile in the doses previously administered to trauma patients, use in the prehospital setting is recommended if patient monitoring and storage requirements can be met.

Potential Benefits:

A cost benefit analysis of TXA use noted that 2,050 patients were entered into the Joint Theater Trauma Registry between October 2003 and June 2009 who received transfusions and met inclusion criteria for the CRASH-2 trial. The overall mortality rate for this cohort was 14.6 percent, which is similar to that reported by the CRASH-2 collaborators. Based on the application of the all-cause mortality RR reduction observed in CRASH-2 (9 percent), if these patients had been treated with TXA, a transfused combat casualty mortality reduction of 1.3 percent is expected. This would translate to 26 additional lives saved at a cost of about \$6,300 per life (one regimen of TXA costs approximately \$80 per patient). For perspective, the cost to the U.S. military of procuring one unit of packed red blood cells is approximately \$100 (excluding the costs of blood storage and shipment to theater, disposables and nursing time associated with blood administration, or blood unit cross-matching).²² The costs of administering TXA are thus substantially lower than the costs of administering one unit of red blood cells. Further, a study using data from the CRASH-2 trial on the cost-effectiveness of TXA concluded that early administration of TXA to bleeding trauma patients would be cost-effective worldwide.²³

RECOMMENDATIONS

SUBJECT: Addition of Tranexamic Acid to the Tactical Combat Casualty Care Guidelines
2011-06

The Board recommends DoD incorporate the following addition to the TCCC Tactical Field Care and Tactical Evacuation Guidelines (before Intravenous Fluids section) regarding bleeding: (proposed additions are italicized within the excerpt below):

If a casualty is anticipated to need significant blood transfusion (for example: presents with hemorrhagic shock, one or more major amputations, penetrating torso trauma, or evidence of severe bleeding):

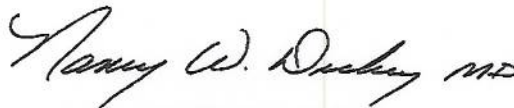
Administer 1 gram of tranexamic acid (TXA) in 100 cc in Normal Saline or Lactated Ringer's as soon as possible but not later than 3 hours after injury.

Begin second infusion of 1 gm TXA after Hextend or other fluid treatment.

Additionally, the Board recommends DoD ensure that ongoing analysis of the use of TXA in theater be a critical element in Performance Improvement measures by the Services.

The above recommendations were unanimously approved.

FOR THE DEFENSE HEALTH BOARD:



Nancy W. Dickey, M.D.
DHB President



Donald Jenkins, M.D.
Chair, Trauma and Injury Subcommittee

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SUBJECT: Addition of Tranexamic Acid to the Tactical Combat Casualty Care Guidelines
2011-06

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